REMARKS

The Examiner provides a number of rejections and we list them here in the order in which they are addressed:

I. Claims 1-3, 7-15 and 19-20 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,888,511 To Skurkovich *et. al.*.

II. Claims 1-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,888,511 To Skurkovich *et. al.* in view of WP 98143209 To Coleman *et. al.*.

I. The Amended Claims Are Novel Over The '511 Patent

The Examiner rejects Claims 1-3, 7-15 and 19-20 under 35 U.S.C. § 102(e) as being anticipated by the U.S. Patent No. 5,888,511 to Skurkovich *et. al* by stating that the reference "... discloses methods of treating autoimmune diseases by administration of antibodies to IL-6 ... anti-TNF ... [and] compositions comprising anti-IL-6 antibodies and antibody to TNF ..." *Office Action, pg 1 ln 12-15.* The Applicant disagrees because Skurkovich *et. al* does not teach each and every element of the preferred embodiment.

A. Skurkovich *et. al.* Does Not Enable The TNF-α/IL-6 Combination

A reference cited by an Examiner under 35 U.S.C. § 102 properly teaches ONLY if it provides clear guidance to one skilled in the art and shows the author had complete possession of the disclosure:

> In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). A reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue,* 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). *MPEP Section 2121.01; Use of Prior Art in Rejections Where Operability Is In Question*

In regards to the present rejection, the Skurkovich *et. al.* specification lacks support for the scope and breadth of Claim 3 and does not place the public in possession of the majority

of combinations. The Skurkovich *et. al.* specification provides only "... a starting point and do[es] not teach the art how to practice the new invention, ... [and therefore does] not constitute anticipation.". *Dewey & Almy Chemical Co. v. Mimex*, 124 F.2d 986, 989 [52 USPQ 138, 141] (C.C.A. 2nd., 1942); *Lincoln Stores, Inc. v. Nashua Manufacturing Company*, 70 USPQ 254 (CA 1 1946).

The Examiner is reminded that the Skurkovich *et. al.* specification provides data on **only ONE** combination. This is an important deficiency in Skurkovich *et. al.* because the Applicant shows that not all of the Skurkovich *et. al.* combinations are effective *in vivo*. Specifically, Example 4 entitled "Failure to Neutralize The *In Vivo* Effects Of Endotoxin By Using Combinations Of Anti-Gamma IFN and Anti-IL-6, Or Anti-Gamma IFN And Anti-TNF" presents such failure data. *Applicants' Specification, pg 13 ln 10-11.* Specifically, the conclusion of Example 4 is stated as;

> The results from Table 3 show that anti-gamma IFN antibody alone as well as combinations of this antibody with 1) antibodies to IL-6, and 2) antibodies to TNF, are **unable to provide significant protection** in the mouse 60 minutes post-challenge. In contrast to the anti-TNF/anti-IL-6 combination therapy, the anti-IFN combination therapies (tested in this example) do not appear to be capable of blocking the downstream cascade. *Applicants' Specification, pg. 14 ln 5-10.* [emphasis added]

The Applicant points out that Example 4 shows that the one, and only, enabled combination (*i.e.*, TNF+INFγ) in Skurkovich *et. al.* is inoperable in the Applicant's preferred embodiment. Therefore, this particular combination disclosed by Skurkovich *et. al.* is irrelevant to the Examiners' anticipation rejection. Furthermore, Skurkovich *et. al.* provides data only for combinations of TNF and INFα/γ and does NOT test the Applicant's antibody combination of TNF and IL-6 (or any other combination of the five cytokines listed in the Markush group of Claim 3). Skurkovich *et. al.* provides data only on the following combinations;

> The patients in Group D were given a combination of anti-TNF-α antibodies+antiIFNα antibodies+anti-IFNγantibodies. *Skurkovich et. al. col 25 ln 4-7.*
>
> Two (2) ml/day each of anti-IFNγ antibodies (3 days) and anti-TNFα antibodies (5 days) were administered parenterally ... *Skurkovich et. al. col 25 ln 4-7.*
>
> ... greater reduction in the clinical manifestations of AIDS disease in patients results from a combined therapy, including the neutralization or removal of IFN α, IFNγ and/or TNF... *Skurkovich et. al. col 29 ln 27-30.*

Furthermore, Skurkovich *et. al.* contains no teachings that provide any evidence, or reasonable expectation, that the untested combinations will work. Example 4 of the present specification demonstrates there are a number of combinations in the "shopping list" of combinations that simply do not work.

A single showing of success for one claimed species does not lead one of ordinary skill to believe that it applied to all other species within that genus. *In re Marzocchi*, 439 F.2d 220,223-24 (CCPA 1971). This point is especially important for claims involving physiological activity. *In re Fisher*, 427 F.2d 833,839 (CCPA 1938) The Applicant argues, therefore, that the enablement in Skurkovich *et. al.* directed only to a single combination having physiological activity amounts to nothing more than an invitation to experiment. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Importantly, the enabled combination taught in Skurkovich *et. al.* is not part of Applicants' Claim 1 or Claim 19. The Applicant respectfully requests the Examiner to withdraw the rejection and pass all pending claims into allowance.

B. Skurkovich *et. al* Does Not Teach Treatment of Sepsis

Skurkovich *et. al* lacks any teaching for the administration of antibodies to TNF-α, IL-6 or gamma IFN, either singly or in any combination, to mammals for the treatment of sepsis. As such, the amended Claim 7 and associated dependent claims, as well as the new Claims 24-33, are novel in regards to Skurkovich *et. al.*. The amendment to Claim 7 is made not to acquiesce to the Examiners' argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application. Applicants hereby expressly reserve the right to prosecute the original (or similar) claims.

The Applicant now respectfully requests the Examiner to withdraw all rejections and pass all pending claims into allowance.

II. Coleman *et al.* Is Not Prior Art

Claims 1-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,888,511 To Skurkovich *et. al.* in view of WO 98143209 To Coleman *et. al.*. The Applicant respectfully disagrees and submits that the Coleman *et. al.* reference is not prior art. The Examiner is referred to the Declaration of Douglas Stafford submitted in Applicants' response to the Office Action mailed February 7, 2001 that presents evidence of

prior conception and reduction to practice. (a courtesy copy is attached hereto) In the present Office Action, the Examiner did not rebut the Stafford Declaration, but instead withdrew the obviousness rejection. Since the Coleman reference is not prior art, Applicant requests that this rejection be withdrawn.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that these grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.252.3353.

Dated: December 24, 2001

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APPENDIX I
MARKED-UP VERSION OF REWRITTEN CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(1)(ii)

7. A method of treatment, comprising:

a) providing:

i) a mammal <u>having symptoms of sepsis</u>,

ii) a therapeutic preparation, comprising anti-TNF-α and anti-IL-6 antibodies; and

iii) administering said preparation to said mammal <u>wherein said symptoms are reduced</u>.